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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,959	10/13/2000	James A. Bibb	600-1-257 CIP	8464

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KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 03/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,959	BIBB ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. Applicant's election with traverse of the invention of group V in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the groups designated by the Examiner fail to define compositions and methods with properties so distinct as to warrant separate examination and search. Applicants have further argued that the search for the invention of the group V and VI would be coextensive since the searches for the methods of groups V and VI would yield similar results. This is not found persuasive because as noted in the previous office action, the inventions of the groups I and II are unrelated as they are drawn to materially different compositions that have different physical and chemical characteristics and also have different utilities. Likewise, the restriction of the inventions I and III is proper since they are related as product and process of use the protein of the group I can be used in many processes other than that of group III, for example, for developing antibodies against the protein. Further the restriction of the inventions of the groups III and VI is proper since the product is not allowable, restriction is proper between said method of making and method of using. The product claim will be examined along with the elected invention (MPEP § 806.05(i)). It is noted that the methods of groups V and VI are directed to the methods of treatment using the agents that modulate the phosphorylation state of Thr75 DARPP-32, and the agents of group V are inhibitors whereas the agents of the group VI are promoters and therefore, agent of group V cannot be used in the invention of group VI. Likewise the agent of group VI cannot be used in the method of group V. Accordingly, claims 16-18 would be examined to the extent they read on the elected invention.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

3. Claims 16-21 are under consideration.

4. Claims 16-18 are objected to because they recited nonelected invention. Applicants are required to amend these claims to reflect the elected invention.

Claim Rejections - 35 USC § 112

5. Claims 16-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention as recited encompasses a method of treatment of any dopamine dysregulation associated condition (such as schizophrenia, Parkinson's disease, Tourette's disease, Huntington's disease, attention deficit hyperactivity and drug abuse) in a patient by administering an agent that inhibits phosphorylation of Thr75DARPP-32. However the specification as filed is not enabling for the claimed invention because there is no evidence of record to indicate that an agent that inhibited DARPP-32 at Thr75 would have treated any disease and neither the specification nor the art of record teaches as to how an artisan of skill would have practiced the claimed method without undue experimentation.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400,

1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

First the major issue is: can a compound that inhibits the phosphorylation of Thr75 of DARPP-32 treat a dopamine dysregulation related disease? It is noted that dopamine is involved in the regulation of a variety of functions, including locomotor activity, emotion and affect, and neuroendocrine secretion. Dopamine functions via specific receptors and there are different classes of dopamine receptors- adenylate cyclase (AC) coupled receptors and AC independent receptors. AC receptors have been further classified into D1 and D2 receptors based on the pharmacology and coupling of the molecules. Of recent D1 and D2 receptors have been further classified into D1 to D5 receptors based on their pharmacology and sequence similarity with D1 or D2 receptors (see Jaber et al. Neuropharmacology 35:1503-1519, 1996). The presence of different receptors is further complexed by the co-expression of various receptors in the same region of the brain and the inability to specifically target a particular receptor subtype by completely selective ligands and this limits studying the signal transduction associated with dopamine receptor. While there have been in vitro studies, Jaber et al cautioned, "Thus, although a dopamine receptor may couple to a particular signally pathway in a cultured cell line, it must be remembered that this may not be the case in vivo, where the same G protein or effectors may not be expressed together with the receptor". In brief, at the time of the invention dopamine mediated signal transduction was not clear in the art and therefore, an artisan of skill would have required extensive experimentation to treat any condition of dopamine dysregulation with any agent and even if there is an effect of an agent in vitro, same effect may not be observed in vivo.

Fienberg et al (Nature 402 :669-671, 1999) noted that CDK5 phosphorylates Thr75 of DARPP-32 using a DARP-32 mutant mouse brain slice or purified protein.

Since dopamine acts via D1 receptors which in turn act via PKA and DARPP-32, even if an agent had effect in vitro on DARPP-32, it would not affect D2 type receptors and therefore, a DARPP-32 phosphorylation inhibitor would not treat a condition that is due to dysregulation of dopamine function via D2 receptors. Furthermore, Greengard (Science 281:838-1030) noted that DARPP-32 phosphorylation dephosphorylation is a complex cascade of events (see figure 2), it is not clear as to how the effect of an agent on DAROPP-32 would be targeted only to one site since same mechanism of signal transduction may be used by multiple molecules and therefore, an agent that inhibits DARPP-32 would not specifically affect dopamine mediated functions. For example, other neurotransmitters such as NMDA, AMPA, GABA, VIP, 5HT4 A2A use the same signal transduction pathway and it is not clear as to how the specificity would be maintained and by inhibiting DARPP-32 phosphorylation these pathways would not be shut off or activated. Again, as noted above even if one saw an effect, the effect may not be there in vivo.

Prior art discloses a DARPP-32 knockout (homozygous) mouse wherein the endogenous DARPP-32 gene has been disrupted so that no DARPP-32 protein is produced in the mouse (Feinberg AA et al. Science 281: 838-842, 1998; Fienberg et al. US 5777195, 7-7-1998). This article also teaches in vitro methods wherein brain slices are incubated for studying the phosphorylation of DARPP-32 or any other substrate (see figures 11-3). Other prior arts by Snyder et al (Snyder et al The Journal of Neuroscience 12:3071-3083), Hemmings et al (Nature 310:503-508, 1984), Girault et al (The Journal of Biological Chemistry 264:21748-21759, 1989) also teach the in vitro method utilizing brain slices. Prior arts on record do not teach the method for treating any diseases or conditions with agents that that inhibit phosphorylation of DARPP-32 or CDK5. It is noted that the specification teaches a rat wherein simultaneous injection of cocaine with roscovitine for 5 days resulted in a change in locomotor activity (see figure 9A-9C). However, it is not clear whether 5 injections of cocaine represent an art recognized drug abuse animal model and therefore, an artisan would not know whether the results of figure 9 are relevant to a patient and whether these results could be extrapolated to a patient.

The specification does not teach whether any other member of indirubin would have produced any changes in any dopamine dysregulation condition.

It is noted that when a compound or an agent is administered to a patient, the compound will be distributed in the entire body of the mouse or to certain locations based on the method of administration. An artisan would not know whether to administer the agent to the patient by oral method or inject by different routes or inject in a particular tissue, particularly in view of the nonspecificity issues. Additionally, an artisan would not know what percent of the administered agent would reach brain and without this information would not be able to determine what doses to use. Furthermore, how would an artisan determine what drugs will readily cross the blood brain barrier? Furthermore, since the agent is to be administered to a patient, the agent may affect other tissues and organs of a mouse and this would produce an accumulated effect on the brain function also. Alternatively, another agent may affect only few organs or tissues, and therefore, the extent of effect of such an agent may be affected by other factors. In other words, an in vivo method would require determination and standardization of numerous steps and parameters and it would require undue experimentation for an artisan to carry out these methods in absence of sufficient guidelines in the prior art or in the specification. Next, what if an agent affects the activity of kinases other than cdk5, the amount of the agent for affecting cdk5 may be limited due to the engagement of the inhibitor with other kinases. For example, Staurosporine, one of the most specific inhibitors of cdk5, also inhibits other kinases including cdc2-like kinases, MAP kinases and protein kinase C (see the discussion in Veerana et al. Neurochemical Research. 21 :629-636, 1996). Therefore, it may phosphorylate a number of peptides or polypeptide that are present in a mouse endogenously, and therefore, there may be a competition for the inhibitory effects of the agent when it is given to a mouse in vivo. The specification does not provide any guidance as to how an artisan of skill would have adjusted the contribution of all the endogenous substrates of cdk5 or effect of cdk5 inhibitors on the kinase activity of all the susceptible kinases. Therefore, the specification does not provide any guidance as to what doses of the agent would have been used in treating a patient, how would

the agent be administered and whether compound would have reached its site of action in amounts sufficient to effect any change in a condition. It is noted that the specification teaches general description of administration routes of administration of a pharmaceutical composition, however no specific information has been disclosed. Courts have stated,

"It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g.,Hybritech Inc. v. Monoclonal Antibodies, Inc. , 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." (See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)).

It is noted that it was not routine in the art to teach a dopamine dysregulation condition using a CDK5 inhibitor, particularly in a situation where CDK5 is a cell cycle regulatory kinase and its inhibition would affect cell division in a general way and it is not clear what would be the outcome of such a treatment when given to a patient.

It is noted that it would have been undue experimentation for an artisan to have practiced the claimed method of treatment because neither the prior art nor the specification teaches as how to treat a patient by administering an inhibitor of DARPP-32 or CDK5 and such a method was not routine in the art and therefore, an artisan would not have been able to predict whether such a treatment would occur.

6. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c).

For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER